REMARKS

Status of the Claims

Claims 1-40 are in the application.

Claims 1-16, 25, 39 and 40 have been withdrawn from consideration.

Claims 17-24 and 26-38 have been rejected.

By way of this amendment, claims 1-16, 25, 32, 34-37 and 39-40 have been canceled, claims 17-22, 24, 26, 27, 30 and 31 have been amended, and new claims 41-44 have been added.

Upon entry of this amendment, claims 17-24, 26-31, 33, 38 and 41-44 will be pending.

Summary of the Amendment

The specification has been amended to replace the term "MyoD" in lines 1-3 of paragraph [0162] with the term "myogenin", which is consistent with the prior made amendment (in December 4, 2006 Response). Applicants submit that the entire paragraph [0162] refers to an experiment detecting myogenin levels in a treated muscle, the results of which are shown in Figure 6, which is labeled "Induction of Myogenin in Skeletal Muscle by IGF-I (3'GH) Plasmid Therapy." Further support for the amendment is found in the brief description of Figure 6 in paragraph [0036]. The title and brief description of Figure 6 are consistent with the amendment. No new matter has been added.

Claim 17 has been amended to more clearly refer to specific embodiments of the invention. Claim 17 has been amended to refer to the "method for stimulating angiogenesis in a subject having an injured muscle." Moreover, claim 17 has been amended to refer to the functional biological equivalents of IGF-1 as having "an amino acid sequence that is at least 85% identical to SEQ ID No.: 4" and that "retains the biological function of stimulating angiogenesis in muscle tissue." In addition, the claim has been amended to more clearly set forth that the "cells of the muscle tissue of the injured muscle of the subject take up the isolated nucleic acid

expression construct" that the "IGF-I or functional biological equivalent thereof is expressed," and that "angiogenesis is stimulated in the muscle tissue of the injured muscle of the subject."

Claim 18-21, 24 and 26 have been amended to more clearly set forth the structural identity of the embodiments defined therein Claim 18 refers to the structure of the myogenic promoter. Claim 19 has been amended to specifically refer to the nucleic acid construct as encoding IGF-1. Claim 20 has been amended to specifically refer to the nucleic acid construct as encoding a functional biological equivalent of IGF-1, such functional biological equivalents of IGF-1 having "an amino acid sequence that is at least 85% identical to SEQ ID No.: 4" and retaining "the biological function of stimulating angiogenesis in muscle tissue." Claim 21 refers to the structure of the 3'UTR. Claims 24 and 26 refer to coding sequences encoding IGF-1 or functional biological equivalents thereof.

Claim 22, 27 and 31 have been amended to more clearly be consistent with the language in amended claim 17.

New claim 41 refers to the structure of the myogenic promoter.

New claim 42 refers to the structure of the 3'UTR.

New claim 43 corresponds to claim 30 but is dependent on claim 19 and therefore incorporates the limitations provided therein.

New claim 44 corresponds to claim 30 but is dependent on claim 20 and therefore incorporates the limitations provided therein.

Support for the amendments is found throughout the specification and claims as filed. No new matter has been added.

Claim Objections

Claims 34-36 have been objected to as being in improperly dependent form for failing to further limit the subject matter of the previous claim. Claims 34-36 have been canceled and the objection is moot.

Objection to the Specification

The Specification has been objected to as containing text inconsistent with data in the figures. The specification has been amended to correct the error. The support for the correction is found in the specification as filed. The basis for the objection has been obviated. Applicants respectfully request that the object be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph
Enablement

Claims 17-24 and 26-38 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. It is asserted that the specification does not provide enablement for the breadth of the claims. Applicants respectfully disagree.

It is acknowledged in the Official Action that the specification enables methods for stimulating angiogenesis in a subject comprising: injecting into a muscle tissue of the subject an isolated nucleic acid expression construct, wherein the muscle tissue comprises cells, wherein the isolated nucleic acid expression construct comprises: a myogenic promoter, a nucleic acid sequence encoding IGF-I and a 3 'UTR, wherein the isolated nucleic acid expression construct is substantially free from a viral backbone; the myogenic promoter, the nucleic acid sequence encoding IGF-I and 3'UTR are operably linked, thereby delivering to the cells of the muscle tissue of the subject the isolated nucleic acid expression construct, thereby expressing said encoded IGF-I in said cells and thereby stimulating angiogenesis in the muscle of said subject.

Claims 19 and 26 (and new claim 43) refer to constructs which correspond to the subject matter acknowledged to be enabled.

The remaining claims, as amended, refer to constructs which encode IGF-1 or functional biological equivalent thereof that have both structural and functional features which would allow

one skilled in the art to practice the invention without undue experimentation. As amended, the claims expressly recite that the constructs encode IGF-1 or functional biological equivalent thereof that have specific biological activity as well as functional features. Those having ordinary skill in the art can readily identify and use functional biological equivalent of IGF-1, as described by the structural and functional features in the claims, without undue experimentation.

It is well settled that Applicants' assertions of enablement must be accepted unless evidence and reasoning is provided which would support a conclusion that one skilled in the art would not believe the objective truth of Applicants' assertions. Nothing in the record supports a conclusion that Applicants' assertions of enablement should not be accepted. The claims recite specific structure and functional limitations which define the claimed subject matter. Those skilled in the art could practice that claimed subject matter without undue experimentation.

Claims 17-24 and 26-38 are in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully request that the rejection be withdrawn.

Written Description

Claims 17-24 and 27-28 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Applicants respectfully disagree.

It is asserted by the Office that the claims contain material which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

As noted above, claims 19 and 26 (and new claim 43) refer to constructs which encode IGF-1 while the remaining claims refer to constructs which encode IGF-1 or functional biological equivalent thereof. As amended, the claims provide both structural and functional features of the functional biological equivalent of IGF-1. These structural and functional features are in the specification as filed and the claims as amended. The specification as filed clearly demonstrates that Applicants were in possession of the subject matter of the claims as

amended. The claimed subject matter is set forth with sufficient structural and functional features to comply with the written description requirement.

Claims 17-24 and 27-28 are in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully request that the rejection be withdrawn.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 18-21 and 24 have been ejected on the grounds of being indefinite. The Examiner states that, as a result of previous amendments, these claims recites "further comprising selecting", which is unclear.

Claim 17 has been amended to recite ".. .comprising the step of:" rather than "...comprising:", for the sake of clarity.

Claims 18-21 and 24 have been amended to remove the phrase "further comprising selecting...", and presenting the subject matter as specific embodiments of the nature of the elements in the claim rather than a method step.

Claims 17-21 and 24, as amended, are clear and definite, and in compliance with the requirements of 35 U.S.C. § 112, second paragraph. Applicants respectfully request that the rejection be withdrawn.

Claim Rejections Under 35 U.S.C. § 102

Claims 17, 19-21, and 31-38 have been rejected under 35 U.S.C. § 102 as being anticipated by Alila et al. *Hum. Gene Therapy* 8:1785-1795, 1997. Applicants respectfully disagree.

In order for a reference to anticipate a claim, every element of the claim must be found, expressly or inherently, in the reference.

Claims 32 and 34-37 have been canceled and the rejection of those claims is moot.

Claim 17 has been amended refer to methods "of stimulating angiogenesis in a subject who has a muscle injury." Claim 17 recites the step of "injecting into muscle tissue of the injured muscle of the subject an isolated nucleic acid expression construct." Claims 19-21, 31, 33 and 238 are dependent on claim 17 and contain each limitation therein.

Nothing in Alila et al. discloses "stimulating angiogenesis in a subject who has an injured muscle." Nothing in Alila et al. discloses "injecting into muscle tissue of the injured muscle of the subject an isolated nucleic acid expression construct." Alila et al. does not anticipate or suggest the claimed invention.

Claims 17, 19-21, 31, 33 and 38, are not anticipated by Alila et al. Applicants respectfully request that the rejection be withdrawn.

Claim Rejections 35 U.S.C. §103(a)

Alila et al in view of van Deutekom et al.

Claims 22-23 have been rejected under 35 U.S.C. § 103(a), as being unpatentable over Alila et al. in view of van Deutekom et al. *Mol. Med. Today*, 214-220,1998. The Applicants respectfully disagree.

Alila et al. is discussed above.

van Deutekom et al. disclose the use of transfection agents.

Claims 22 and 23 are dependent on claim 17 and further limit the claim with the step of mixing the isolated nucleic acid expression construct with a transfection-facilitating system before delivering the isolated nucleic acid expression construct into the muscle tissue of the injured muscle of the subject (claim 22). According to claim 23, the transfection-facilitating system is a liposome or a cationic lipid.

As noted above, claim 17 refers to methods "of stimulating angiogenesis in a subject who has an injured muscle" by "injecting into muscle tissue of the injured muscle of the subject an

isolated nucleic acid expression construct" as set froth in the claim. Alilo neither teaches nor suggests stimulating angiogenesis in a subject who has an injured muscle" by "injecting into muscle tissue of the injured muscle of the subject an isolated nucleic acid expression construct." Nothing in van Deutekom et al. teaches nor suggests stimulating angiogenesis in a subject who has an injured muscle" by "injecting into muscle tissue of the injured muscle of the subject an isolated nucleic acid expression construct" as set forth in claim 17. The combination of Alilo et al. and van Deutekom et al. does not yield the present invention.

Claims 22-23 are not rendered obvious by the combination of Alilo et al. and van Deutekom et al. Applicants respectfully request that the rejection be withdrawn.

Alila et al in view of Draghia-Akli et al., Fewell et al. and Isner et al.

Claims 18, 24, and 26-30 have been rejected under 35 U.S.C. § 103(a), as being unpatentable over Alila et al. in view of Draghia-Akli et al., Fewell et al. and Isner et al. Applicants respectfully disagree.

Alila et al. is discussed above.

Draghia-Akli et al. is asserted to disclose expression constructs comprising myogenic promoter linked to coding sequences for human growth hormone releasing hormone. The constructs are injected intramuscularly into pigs followed by electroporation and taken up by muscle cells where the coding sequences are expressed to produce human growth hormone releasing hormone.

Fewell et al. is asserted to disclose expression constructs complexed with polyGlutamate polypeptides that are injected intramuscularly into mice followed by electroporation. The constructs encode Factor IX or EPO. The constructs are taken up by muscle cells where the coding sequences are expressed to produce Factor IX or EPO.

Isner et al. is asserted to disclose stimulating angiogenesis in ischemic muscle by injecting an expression construct that encodes an angiogenic protein including IGF-1.

The combination does not produce the claimed invention. Moreover, one skilled in the art would not combine the references to produce the claimed invention.

The combination of Alila et al., Draghia-Akli et al., Fewell et al. and Isner et al. does not produce the present invention. None of the references teach or suggest stimulating angiogenesis in a subject who has a muscle injury. Alila et al. refers to nerve regeneration following nerve injuries. Isner et al. discloses treatment of ischemic muscles. Draghia-Akli et al. refers to systemic delivery of growth hormone releasing hormone by intramuscular delivery of nucleic acid constructs that encode GHRH. Fewell et al. refers to delivery of Factor IX to plasma by intramuscular delivery of nucleic acid constructs that encode Factor IX. The references are silent with respect to stimulating angiogenesis in a subject who has a muscle injury.

One skilled in the art would not combine the references to produce the claimed invention. Alila et al. and Isner et al. are both focused on localized effects of the IGF-1. Alila et al. expressly states that the methods disclosed therein are particularly useful because the IGF-1 produced does not have systemic effects. Thus, according to Alila et al., the methods is particularly useful because it avoids toxicity and side effects produced by recombinant administration of IGF-1, which effect is not localized but instead systemic. On the other hand, both Draghi-Akli et al. and Fewell et al. both use electroporation mediated gene transfer to achieve system delivery. The aim of each of Draghi-Akli et al. and Fewell et al. is to deliver protein beyond the muscle which is completely contrary to the teachings of Alila et al. One skilled in the art would not combine Alila et al with either of Draghi-Akli et al. or Fewell et al. because Alila et al. clearly teaches the desirability of limited local protein distribution and away from systemic distribution. One skilled in the art would not combine the teachings in view of Alila et al teaching away from such a combination.

Claims 18, 24, and 26-30 are not rendered obvious by the combination of Alilo et al. and in view of Draghia-Akli et al., Fewell et al. and Isner et al. Applicants respectfully request that the rejection be withdrawn.

Conclusion

For the foregoing reasons, Applicants respectfully urge that claims 17-24, 26-31, 33, 38 and 41-44 are in condition for allowance. A Notice of Allowance is earnestly solicited.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully Submitted,

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Dated: September 6, 2007

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